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ALISA A. HARBIN
CHIRON CORPORATION
4560 HORTON STREET
M/S R-338
EMERYVILLE, CA 94608-2916

EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/521,139	Applicant(s) PRESTRELSKI ET AL.	
	Examiner Humera N. Sheikh	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *11-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Associate Power of Attorney letter filed 10/27/03, the Petition under 37 C.F.R. §1.137(b) (granted), The Information Disclosure Statement (IDS) and the Amendment, all filed 02/12/04 is acknowledged.

Claims 1, 2, 4-10 and 27 are pending. Claims 1, 2, 5 and 6 have been amended. New claim 27 has been added. Claims 11-26 have been previously withdrawn. Claim 3 has been cancelled. Claims 1, 2, 4-10 and 27 are rejected.

The claim objection for claim 5, the 35 U.S.C. 112 2nd paragraph rejection (for claim 6), the 35 U.S.C. §102(a) & (e) rejections for Bellhouse *et al.* ('796) and Edwards *et al.* ('064) have been *withdrawn* by virtue of the Amendment.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4-10 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bellhouse *et al.* in view of Tice *et al.* (US Pat. No. 4,530,840).

Bellhouse et al. teach drug-containing particles that are delivered through a needleless syringe, wherein the particles comprise a therapeutic agent in controlled doses into the skin and wherein the particles have a particle size in the range of 0.1 to 250 microns, a diameter of up to 100 microns and a density in the range of 0.1 to 25 g/cm^3 (see reference col. 1, lines 30-44); (col. 4, lines 13-50). Bellhouse et al. also teach a needleless syringe for transdermal delivery comprising particles of a therapeutic agent wherein the syringe may be used for routine delivery of drugs (i.e., insulin for the treatment of diabetes), used for immunization and for the delivery of slow-release drugs (i.e., painkillers and contraceptives). The needleless syringe may also be used for the delivery for genetic material into living skin cells, muscle, blood or lymph and organs (col. 1, lines 45-54). The needleless syringe can also be used for surgical procedures to deliver drugs and biologics to organ surfaces, solid tumors and/or to surgical cavities.

The instant invention is drawn to a particulate composition suitable for administration to a subject by means of a needleless syringe, wherein the composition comprises particles that comprise a biologically active agent and a biodegradable sustained-release material wherein the particles have a mean mass diameter of from about 20 to about 75 microns and an envelope density of from about 0.8 to about 1.5 g/cm^3.

Bellhouse et al. teach a drug-containing particulate composition delivered by a needleless syringe wherein the particles comprise a therapeutic agent in a slow-release rate and he explicitly teaches that the drug-containing particles

have a particle size in the range of about 10 to 250 microns and a density in the range of 0.1 to about 25 g/cm^3 (see claim 1).

There is no significant distinction observed between the prior art and the instant invention since the prior art similarly teaches such a particulate composition comprising an active agent wherein the particle density (0.1 to about 25 g/cm^3) and particle size or diameter (~ 10-250 microns), which clearly read on the applicant's instant claims.

Bellhouse *et al.* refer to the particles as having a particle *diameter* and does not specifically state, "*mean mass aerodynamic diameter*", however since the particles of Bellhouse et al. are intended for a similar purpose and are formulated in a similar manner as the applicant, one of ordinary skill familiar in the pharmaceutical art would interpret the particle diameter as taught by Bellhouse, as referring also to the mean mass diameter. Furthermore, since the formulation of the particles of the prior art is similar to those of the instant invention, the properties would also be the same. The expected result would be a particulate composition with a predetermined mass diameter for the desirability of obtaining the best possible outcome.

Bellhouse *et al.* are deficient only in the sense that they do not teach the specified sustained-release materials (poly- lactide, glycolide, caprolactone, hydroxybutyrate, etc) as claimed by the applicant.

Tice *et al.* teach an injectable long-acting, slow-release microparticle formulation for the delivery of anti-inflammatory agents comprising suitable

polymeric matrix materials, which include poly (glycolic acid), poly-d, l-lactic acid, copolymers thereof, polycaprolactone, poly (lactic acid-caprolactone) and the like (see reference col. 2, lines16-55). Table I demonstrates a method for the preparation of methylprenisolone acetate microparticles with a poly (d, l-lactide) excipient (col. 5, line 52 through col. 6, line 68).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made and there is ample motivation provided by the prior art to incorporate the suitable polymeric matrix materials such as poly (glycolic acid), poly-d, l-lactic acid, copolymers thereof, polycaprolactone, poly (lactic acid-caprolactone) and the like, because the prior art teaches that these polymeric matrix materials are suitable polymeric materials for obtaining biocompatibility and biodegradability with the human body.

Further motivation is provided by the prior art since Tice et al. teach a slow-release injectable microparticle formulation wherein an appropriate selection of polymeric materials yields a microparticle formulation exhibiting both diffusional and biodegradation release properties. The expected result would be a slow-release, biodegradable and biocompatible microparticle formulation, as similarly desired by the applicant.

This rejection is maintained and applied to newly added claim 27.

The prior art teaches a sustained release particulate composition whereby various active agents are delivered through needleless syringe technology.

Claims 1, 2, 4-10 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards *et al.* (US Pat. No.5,874,064).

Edwards *et al.* teach improved aerodynamically light particles for drug delivery comprising particles capable of a long-term release of a therapeutic agent, having a tap (envelope) density less than 0.4 g/cm^3 and a mass mean diameter between 5 microns and 30 microns. The particles may be formed of biodegradable and biocompatible materials such as biodegradable polymers, proteins, or other water-soluble materials (see Abstract); (col. 3, lines 12-40); (col. 5, lines 8-33). The therapeutic agent can be selected from the group consisting of proteins, polysaccharides, lipids, nucleic acids and combinations thereof (claim 13). The aerodynamically light particles may be fabricated or separated to provide a particle sample with a preselected size distribution. For example, greater than 30%, 50%, 70% or 80% of the particles in a sample can have a diameter within a selected range of at least 5 microns. The selected range within which a certain percentage of the particles must fall may for example, between about 5 and 30 microns, or optionally between 5 and 15 microns (col. 4, lines 10-47). The particles may be formed from any biocompatible biodegradable polymer, copolymer or blend, which is capable of forming particles having a tap (envelope) density less than about 0.4 g/cm^3 (col. 6, lines 39-43). Edwards teaches that bulk-eroding polymers can be used, which include polyglycolic acid (PGA) or polylactic acid (PLA) or copolymers thereof.

Various other polymers are also taught (col. 6, line 50 through col. 7, line2). Examples 5 and 6 demonstrate the use of two particle types using light and non-light particles (cols. 15 & 16).

The instant invention is drawn to a particulate composition suitable for administration to a subject by means of a needleless syringe, wherein the composition comprises particles that comprise a biologically active agent and a sustained-release material wherein the particles have a mean mass diameter of from about 20 to about 75 microns and an envelope density of from about 0.8 to about 1.5 g/cm^3.

The prior art teaches improved aerodynamically light particles for drug delivery comprising particles capable of a long-term release of a therapeutic agent, having a tap (envelope) density less than 0.4 g/cm^3 and a mass mean diameter between 5 microns and 30 microns.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate a particulate composition comprising aerodynamically light particles containing a drug or therapeutic agent with biodegradable and biocompatible sustained release materials having a tap density less than 0.4 g/cm^3 and a mass mean diameter between 5 microns and 30 microns because they particles are then capable of a longer term release of a therapeutic agent and (due to the relatively low tap density) subsequently undergo slow degradation and drug release. The expected result would be improved aerodynamically light particles for drug delivery offering effective biodegradable and biocompatible capabilities.

This rejection is maintained and applied to newly added claim 27.

Edwards et al. teach the delivery of injectable aerodynamically light particles for drug delivery whereby a wide variety of therapeutic agents are employed (see col. 10, lines 1-21).

Response to Arguments

Applicant's arguments filed 02/12/04 have been fully considered.

Firstly, the Applicant argued regarding the claim objection for claim 5, (misspelling of poly-caprolactone). Applicants have amended claim 5 to correct spelling. Accordingly, the claim objection has been *withdrawn*.

Next, the Applicant argued regarding the 35 USC §112 2nd paragraph rejection for claim 6. Applicants have amended claim 6 for clarification purposes. Accordingly, the indefiniteness rejection for claim 6 has been *withdrawn*.

The Applicant argued regarding the 35 USC §102(a) & (e) rejections of claims 1-4 and 7-10 over Bellhouse et al.('796), stating, "Bellhouse et al. does not disclose or teach particulate compositions composed of a biological active agent in association with a biodegradable sustained-release material, such as a poly(lactide), poly(glycolide), poly(caprolactone)....and poly(lactide-co-caprolactone). It does not follow that eh encapsulating shell must be composed of a biodegradable sustained-

release material as claimed in claim 1. Bellhouse does not disclose each and every claimed element."

These arguments have been fully considered and were found to be persuasive by virtue of the Amendment. Accordingly, the 35 USC §102(a) & (e) rejections of claims 1-4 and 7-10 over Bellhouse et al. have been *withdrawn*.

Next, the Applicant argued regarding the 35 USC §102(a) & (e) rejections of claims 1-8 over Edwards et al. ('064) stating, "Edwards by contrast discloses aerodynamically light particles, where at least approximately 90% of the particles have a mass mean diameter between 5 and 30 microns and where the particles have an aerodynamic diameter of between one and three microns and a tap density of less than $0.4g/cm^3$. Edwards does not disclose or teach particles that have an envelope density of from about 0.8 to about $1.5g/cm^3$ and thus Edwards does not teach each and every limitation of the particulate composition set forth in claim 1."

These arguments have been fully considered and were found to be persuasive by virtue of the Amendment. Accordingly, the 35 USC §102(a) & (e) anticipation rejections of claims 1-8 over Edwards et al. have been *withdrawn*.

The Applicant then argued regarding the 35 USC §103(a) rejection of claims 1-4 and 6-10 over Bellhouse et al. alone, stating, "Bellhouse does not disclose the use of a biodegradable sustained release material and the Examiner has not made out a *prima facie* case of obviousness. Bellhouse does not provide any motivation to modify the particles disclosed in the reference, nor does it convey a reasonable expectation of success."

These arguments have been carefully considered and were found to be persuasive by virtue of the Amendment. Accordingly, the rejection has been

withdrawn and reformulated as Bellhouse *et al.* in view of Tice *et al.* for all claims 1, 2, 4-10 and 27.

Next, the Applicant argued in regards to the 35 USC §103(a) rejection of claim 5 over Bellhouse et al. in view of Tice et al. stating, "Tice is not directed to a particulate composition suitable for administration to a subject by means of a needleless syringe, but rather is directed to a composition that is administered via a standard syringe and needle. Tice does not disclose the use of poly(hydroxybutyrate). Examiner has not made out a *prima facie* case of obviousness."

These arguments have been considered. The rejection has now been reformulated as Bellhouse *et al.* in view of Tice *et al.* for all claims 1, 2, 4-10 and 27.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Bellhouse et al. teach drug-containing particles that are delivered through a needleless syringe wherein the particles have a particle size in the range of 0.1 to 250 microns, a diameter of up to 100 microns and a density in the range of 0.1 to 25 g/cm^3 (col. 1, L. 30-44); (col. 4, L. 13-50).

Bellhouse et al. are lacking only in the sense that they do not explicitly teach the selective list of biodegradable polymers as claimed in claim 5 (i.e., poly(lactide), poly(caprolactone),etc.). Tice et al. resolves this only deficiency of Bellhouse et al. by teaching an injectable long-acting, slow-release microparticle formulation comprising suitable polymeric matrix materials that include poly (glycolic acid), poly-d, l-lactic acid, copolymers thereof, polycaprolactone, poly (lactic acid-caprolactone) and the like (see for instance col. 2, lines16-55). Therefore ample motivation is provided by the prior art and a *prima facie* case of obviousness has been properly established by the Examiner since the art teaches needless syringe compositions comprising similar or overlapping diameter and density ranges. The Applicants' argument that Tice administers via a standard syringe and needle, rather than a needless syringe is not persuasive since the primary reference of Bellhouse et al. initially teaches the use of a needleless syringe. It is therefore not deemed necessary that Tice et al. also teach administration of a drug through a needleless syringe. Tice et al. teach injectable compositions comprising similar ingredients in the same field of endeavor as instantly being claimed. The Applicant's argument that Tice does not disclose the use of poly(hydroxybutyrate) is not persuasive since instant claim 5 is a Markush grouping claim (i.e., selected from the group consisting of) and hence only requires the selection of one ingredient from those listed and Tice et al. teach various biodegradable polymeric materials as seen in column 2, lines 50-55. Hence, Applicants' arguments were not persuasive in these regards.

Lastly, the Applicant argued regarding the 35 USC §103(a) rejection of claims 1-8 over Edwards et al. ('064) stating, "Edwards does not disclose a particulate composition with a mean mass aerodynamic diameter of from about 20 to 75 microns and an envelope density of from about 0.8 to about 1.5 g/cm^3. The Examiner has not made a *prima facie* case of obviousness. In addition, Edwards does not disclose the use of poly(caprolactone) or poly(hydroxybutyrate) nor does it disclose a particulate composition having a first set of particles comprising biologically active agent in association with a first sustained-release material and a second set of particles comprising biologically active agent in association with a second sustained-release material, wherein the second sustained-release material releases the active drug at a different rate than the first sustained-release material as claimed in claim 6. Edwards provides no motivation to modify the disclosed particles to arrive at the claimed invention. Contrastingly, the particles disclosed in Edwards need to be smaller and to have a lower density. Edwards teaches away from the high density particles required for needleless delivery claimed by stating that 'diminishing the tap density of the particles by increasing particle surface irregularities and particle porosity permits the delivery of larger particle envelope volumes into the lungs' col. 5, L. 54-57. Thus, special measures are taken to ensure that small, light particles are used. Such small light particles would not be suitable for use in the needleless syringe technology."

These arguments have been fully considered but were not found to be persuasive. Edwards et al. teach improved aerodynamically light particles for drug delivery comprising particles capable of a long-term release of a therapeutic agent, having a tap (envelope) density less than 0.4 g/cm^3 and a mass mean diameter between 5 microns and 30 microns. The particles may be formed of

biodegradable and biocompatible materials such as biodegradable polymers, proteins, or other water-soluble materials. Applicants now claim a particulate composition with a mean mass aerodynamic diameter of from about 20 to 75 microns and an envelope density of from about 0.8 to about 1.5 g/cm^3. The mean diameter taught by Edwards, as delineated above, is between 5 microns and 30 microns, which is an overlapping amount that clearly reads on the instant diameter range. A review of the Applicant's specification indicates up to 250 microns size particles are permitted and taught by the prior art. Applicant now specifies less than 250 micron size. For drug delivery, Applicant's specification on pg. 31 teaches a size of 10-100 microns. With regards to the mean diameter and tap (envelope) density, the amounts claimed have not been established as being critical. Edwards teaches a density less than 0.4 g/cm^3. One of ordinary skill in the art would be capable of determining suitable amounts through routine or manipulative experimentation, to obtain the best possible outcome. The Examiner has established a *prima facie* case of obviousness, since the prior art clearly teaches an injectable particulate composition for drug delivery. Since the prior art is in the same field of endeavor and solving the same problem, no invention is seen in the optimization of well-known sizes or ranges. The Applicant's argument that 'Edwards does not teach the use of poly(caprolactone) or poly(hydroxybutyrate) nor does it disclose a particulate composition having a first set of particles comprising biologically active agent in association with a first sustained-release material and a second set of particles comprising biologically active agent in association with a second sustained-release material' is also not persuasive since Edwards does

teach a controlled release injectable particulate composition, comprising various polymers and copolymers (col. 6, lines 51-57). Regarding the argument of first and second set of particles, the arguments are not persuasive since particles generically are suggested by the prior art. One of ordinary skill in this art would recognize particles per se as being suitable in drug delivery formulations and the fact that Applicant recites a set of particles, first and second set, does not patentably define over the generic teaching of the reference since the prior art solves the same problem and is in the same field of endeavor. The burden is shifted to applicant to show results that accrue only from the presence of sets of particles over the expected results suggested by the prior art.

Hence, the instant invention remains obvious and unpatentable over the prior art of record.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory

action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

hns H.N.S.

June 14, 2004

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600